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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
AKHAVAN, RAMIN	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 08/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Applicant 08/09/04 RA

Office Action Summary	Application No.	Applicant(s)	
	09/600,521	DONG ET AL.	
	Examiner	Art Unit	
	Ramin (Ray) Akhavan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *47,58-61,66-73 and 113-119* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47,58-61,66-73 and 113-119* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

An amendment filed, 05/24/2004, is acknowledged and entered. As a result, claims 47, 58, 60-61, 66, 68 and 70 are amended and new claims 113-119 are added. Claims 47, 58-61, 66-73 and 113-119 are pending and under consideration in this action. All objections and rejections not repeated herein are hereby withdrawn. Where applicable, Applicant's arguments are addressed in the body of the rejection, under "Response to Arguments". As additional grounds for rejection are set forth, **this action is NON-FINAL**.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 118 and 119 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

The claims contain subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. More specifically, claims 118 and 119 are drawn to or encompass adenoviral vectors. The application discloses the methods which necessarily require the vectors for successful practice, where said vectors are encompassed by the definitions for **biological material** set forth in 37 C.F.R. § 1.801.

Because it is apparent that these biological materials are essential for practicing the claimed invention, they must be obtainable by a reproducible method set forth in the specification or otherwise be known and readily available to the public as detailed in 37 C.F.R. §§ 1.801 through 1.809.

It is unclear whether this biological material is known and readily available to the public or that the written instructions are sufficient to reproducibly construct this biological material from starting materials known and readily available to the public. Accordingly, availability of such biological material is deemed necessary to satisfy the enablement provisions of 35 U.S.C. § 112. If this biological material is not obtainable or available, the requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the biological material. In order for a deposit to meet all criteria set forth in 37 C.F.R. §§ 1.801-1.809, applicants or assignee must provide assurance of compliance with provisions of 37 C.F.R. §§ 1.801-1.809, in the form of a declaration or applicant's representative must provide a statement. The content of such a declaration or statement is suggested by the enclosed attachment. Because such deposit will not have been made prior to the effective filing date of the instant application, applicant is required to submit a verified statement from a person in a position to corroborate the fact, which states that the biological material which has been deposited is the biological material specifically identified in the application as filed (37 C.F.R. § 1.804). Such a statement need not be verified if the person is an agent or attorney registered to practice before the Office. Applicant is also reminded that the specification must contain reference to the deposit, including deposit (accession) number, date of deposit, name and address of the depository, and the complete taxonomic description.

2. Claims 47, 58-61, 66-73 and 113-119 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *in vitro* use of apoptosis-mediated cancer cell death, does not reasonably provide enablement for *in vivo* use.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to *use* the invention commensurate in scope with these claims. All the claims recite "cancer cell" or "tumor" and are directed to destruction of such malignant cells, thus read on gene therapy and *in vivo* use. The test for enablement is whether one skilled in the art could make use the claimed invention from the disclosure in the specification coupled with information known in the art without undue experimentation. *United States v Telectronics Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor but instead is a conclusion reached by weighing many factors which are outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). The factors include the following:

Scope/Breadth of the claims. The scope/breadth of the claims are broad, where the claims are drawn to a process of inducing cell death involving transfection of any cell *in vivo* expressing any apoptosis-mediating receptor, with any expression vector, which encode any apoptosis-mediating ligand. More particular claims are drawn to the Fas/FasL (receptor/ligand) pathway for inducing apoptosis.

Nature of the invention. The invention is primarily based on a process involving gene therapy, where a replication-deficient adenoviral vector encoding an apoptosis signaling ligand, such as FasL, is used to transfect cells, with subsequent regulated expression (e.g. via the Tet-responsive regulatory element or tissue-specific promoters) of the ligand in cells that may

express the Fas receptor. Put another way, the Fas/FasL apoptosis pathway is directed toward inducing death in cancer cells. The claims read on *in vivo* use, i.e., eradication of cancerous cells or tumors, including in any subject (e.g. immunocompetent patient).

State of the art/ Unpredictability of the art. The invention is directed to *in vivo* gene therapy and specifically to targeting tumor cells expressing Fas receptor using an adenoviral expression construct encoding FasL. With regard to gene therapy, the state of art is also poorly developed. "...there is still no conclusive evidence that gene-therapy protocol has been successful in the treatment of a human disease." (*See*, Anderson, Nature, 1998; 392: 25-30, at 25). Gene therapy is still a highly unpredictable art within biology and medicine. For example, nucleic acids encoding therapeutic products may be erroneously inserted, thus disrupting a particular gene resulting in unknown, adverse or detrimental effects. (*See*, Check, E., Nature, 2003;421: 678) (citing occurrence of leukemia due to insertion nucleic acids used in gene therapy into a particular stretch of DNA); (*See also*, Juengst, ET. BMJ, 2003;326:1410-11;indicating that gene transfer often has multiple and unpredictable effects on cells).

In addition, with regard to adenoviral vectors for targeting tumor targeting *in vivo*, there is a substantial risk of vector immunogenicity, such as localized inflammation that can occur at the site of gene transfer due to T- or B-Cell mediated targeting of transduced cells. In addition, both neutralizing (which would hinder expression of the therapeutic gene; i.e. FasL) and non-neutralizing anti-adenovirus antibodies are capable of activating complement. (*See supra*, Green and Seymour, at 1039, col. 2, ¶ 2). Furthermore, with regard to use of adenoviral vectors in tumor targeting, there are significant hurdles that need to be overcome: infection of or transfer to non-target cells, evasion of neutralization by anti-adenoviral antibodies, viral interaction with

blood cells, immune parameters affecting efficacy and toxicity and viral bio-distribution. (*See*, Green and Seymour. Cancer Gene Therapy; 2002;9:1036-42, pp. 1039-40).

In addition, while the Fas and FasL mediated pathway for apoptosis is well characterized, studies conducted with regard to targeted inducement of cell death have been exclusively *in vitro* or in immunocompromised mice. (See e.g., Arai et al. *Gene transfer of Fas ligand induces tumor regression in vivo*. Proc. Natl. Acad. Sci. Dec. 1997;94:13862-7; showing apoptosis of renal and colon carcinoma tumors implanted into flanks of nude mice, where tumors were injected with adenoviral vectors expressing FasL). More importantly, clinical studies studying the therapeutic effect of FasL in killing cancer cells were disappointing due to "severe toxicity observed in preclinical studies". (*See*, Rossi and Gaidano. Haematologica/J. Hematology, 2003; 88(2):212-18, at 217).

Moreover, Fas receptors are widely expressed by many non-cancerous cells in the body, therefore extending the potential for toxicity to different tissue/organs. Therefore, FasL expression could have deleterious effects on normal cells expressing Fas receptor (e.g. hepatocytes). This can occur whether transfected cancer cells express with subsequent systemic delivery to non-target sites or whether non-target cells are transduced and express FasL. In regard to hepatotoxicity, because there are a substantial number of Fas receptors expressed in liver cells, such cells/tissue would be susceptible to FasL mediated apoptosis. Notwithstanding regulatable FasL expression, *in vitro* results do not necessarily translate into *in vivo* use. For example, having even a base line level of FasL expression or "leaky" expression can result in unintended toxic effects, making practice of invention unpredictable. Furthermore, if viral vectors enter the systemic system, whether expressing FasL or not, they can be delivered to other

cells exacerbating the immune response. Therefore, it would follow that there is a great deal of unpredictability as to whether expression of FasL *in vivo* would result in cell death in cancer cells expressing Fas receptor. In sum, the state of art, with respect to *in vivo* expression of a ligand in a ligand-receptor mediated (e.g. Fas-FasL) apoptosis, is still developing with many substantial concerns and question yet to be resolved.

In addition, expressing FasL may have unintended deleterious effects on the subject's anti-cancer defense. One such effect is tumor immune privilege; this occurs where intra-tumoral lymphocytes, such as natural killer cells (the main anti-tumor effector cells, which highly express Fas receptor) are actually "attacked" by cancer cells that express FasL. (*See*, O'Connell et al. Nature Med., 1999;5(3):267-8, at 267). This is relevant to the instant invention because in regard to the claimed embodiments, the FasL expressed could in effect "attack" the natural killer cells, i.e., non-target cells, thus injecting further unpredictability with respect to *in vivo* practice of the claimed invention. Of course, safety and efficacy are not enablement requirements, but certainly are factors that exacerbate unpredictability with regard to practicing the invention.

In sum, it must be deemed that there is a great deal of unpredictability that is attendant with practicing the claimed invention *in vivo*.

Amount of guidance provided/working examples. The specification provides a single example replication-deficient adenoviral vector expressing a murine FasL (i.e. rAD/FasL-GFP_{TETd}) that results in apoptosis of cells expressing the Fas receptor, *in vitro* cell culture and *in vivo* in immunocompromised mice, where breast cancer and prostate cancer cell lines are deposited in nude mice. In addition the disclosure indicates experiments involving

immunocompetent dogs were conducted, but there are no results set forth. (Spec. pp. 39-40, "Toxicology...beagles").

The examples do not provide any significant guidance with respect to unpredictability in practicing the claimed invention in *in vivo* in an immunocompetent subject. For example, there is no significant guidance provided with respect to circumventing obstacles such as immunotoxicity and immunoneutralization that would be attendant with *in vivo* application in human subjects. Furthermore, there is no relevant or significant guidance provided with respect to obstacles and unpredictability in regard to FasL expression in non-target cells, for example. Moreover, no other combinations of receptor/ligand are taught in the instant specification, *in vivo* or otherwise.

Amount of experimentation required. The level of skill in the art required to practice the claimed invention is high. Given the unsolved hurdles to successfully practicing the invention, the level of unpredictability in the art and lack of working examples *in vivo* with immunocompetent subjects, as outlined above, it must be considered that the skilled artisan would be required to conduct trial and error experimentation of an undue, unpredictable nature in order to attempt to practice the claimed invention commensurate with claims' scope. Applicant should note, that obstacles and hurdles to successful practice may inhere safety and efficacy concerns, but nonetheless are relevant, only in so far as they prevent one of skill to *use* the invention commensurate with the scope of the claims.

Response to Arguments

Applicant's arguments in regard to obviating the enablement rejection are not deemed persuasive. Applicant argues on two grounds. First, Applicant submits that, "While curing

cancer by gene therapy is a potential utility of the claimed invention, this particular utility is not being claimed." (Remarks, p. 8, ¶ 1). Therefore, Applicant argues that the enablement requirement should not be measured against unclaimed utilities. As indicated above, the claims read directly on *in vivo* use (See supra, Nature of the invention; See also, claims 58-60, 66-67; particularly directed to *in vivo* use). Furthermore, the specification clearly contemplates *in vivo* use or gene therapy. (e.g. Spec., p. 3, l. 15; p. 4, l.26; ; p. 5, l. 3; p. 6, l. 28; p. 20; ll. 5-30; p. 21, ll. 17-30). That the claims also read on *in vitro* use does not necessarily obviate a scope of enablement rejection (e.g. claim 1 reads on both *in vitro* and *in vivo* practice for the invention). Therefore gene therapy or *in vivo* use *is* a claimed utility.

Applicant also asserts that the Examiner requires an *in vivo* example in order to satisfy the enablement requirement. Furthermore, Applicant asserts that Applicant cannot be required to provide an *in vivo* example, correctly indicating that an enablement requirement does not turn on whether an example is disclosed. (Remarks, p. 8, ¶ 2). The lack of relevant examples is but one factor that is considered on whole with other factors in satisfying the enablement requirement. Put another way, the lack of example(s), when considered in totality with the other factors under the enablement requirement, merely shows the high degree of unpredictability and the likelihood of the great deal of undue experimentation that would be required, for one of ordinary skill in the art to *use* the claimed invention. Therefore, whether or not a relevant *in vivo* example is disclosed is not by itself dispositive as to whether the enablement requirement is satisfied.

In addition, Applicant submits Exhibit A (FasL-mediated death of human breast cancer cells transplanted in nude mice), as evidence that one of skill could use the invention *in vivo*. However, as noted in the Action filed, 02/18/2004, as well as above, an immunocompetent

model would not address concerns such as immunotoxicity or immunoneutralization (e.g. in regard to adenoviral vectors), which in turn present obstacles to successful practice of the claimed invention. Furthermore, an immunocompromised model system would not address obstacles presented such as the unpredictability of FasL expression in non-target cells (e.g. hepatocytes) or delivery of FasL to unintended cells/tissue. In sum, Applicant's arguments appear to be directed to claim interpretation and a single *Wand's* factor cited in the enablement rejection. The claims read on *in vivo* use and the factors under the enablement requirement should be examined as a whole in determining whether one of skill can make and *use* the invention commensurate with the scope of the claims. Therefore, the enablement rejection is maintained.

New Grounds of Rejection

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 47, 58-61 and 113-114 rejected under 35 U.S.C. 102(a) as being anticipated by Leon et al. (Arai et al. PNAS, 1997; 94 :13862-67 ; see whole document which was provided to Applicant previously).

The claims are drawn to a method for inducing cell death in cancer cells, via a ligand-receptor mechanism mediating apoptosis, where the ligand is expressed via an adenoviral vector and where the target cells express a receptor that specifically binds the ligand. More particularly, the ligand is FasL and the receptor is Fas. Furthermore, the term "solid tumor" is interpreted as b broadly as reasonable, to include a localized foci of cancer cells/tissue.

Arai et al. teach a method for adenoviral-mediated gene transfer into tumor cells. More particularly, an adenoviral vector encoding FasL (ADV-FasL) is used to transduce renal carcinoma cells (Renca cells) expressing Fas. (e.g. Abstract; p. 13862, under "Cells"; p. 13863, col. 1, under "Adenovrial Vectors" and "Animal Experiments"). Furthermore, ADV-FasL is injected using a hypodermic needle directly into a tumor mass. (e.g. p. 13863, col. 1, ¶ 5). Transduction with ADV-FasL led to massive cell death (apoptosis) in tumor tissue. (e.g. p. 13863, col. 2, ¶ 2 bottom). In sum, Arai et al. anticipate the rejected claims.

4. Claims 47, 58-61, 115 and 116 are rejected under 35 U.S.C. 102(b) as being anticipated by Eicher et al. (Clin. Can. Res., Oct. 1996; 2:1659-64; see whole document).

The claims are drawn to a method for inducing cell death in cancer cells, via a ligand-receptor mechanism mediating apoptosis, where the ligand is expressed via an adenoviral vector and where the target cells express a receptor that specifically binds the ligand. The term "solid tumor" is interpreted as b broadly as reasonable, to include a localized foci of cancer cells/tissue. In addition, claims are directed to the vector comprising a reporter, more particularly where the reporter and ligand are encoded as a fusion protein.

Eicher et al. teach a method of gene therapy comprising transduction of cancer cells/tissue with an adenoviral vector. (e.g. Abstract). More particularly, the cancer cells are of head and neck origin. (e.g. p. 1659, col. 2, under "Cell Lines"). The adenoviral vector encodes an apoptosis signaling ligand (p53; an apoptosis mediating ligand), which is further encoded as a fusion protein with a reporter (FLAG). (e.g. p. 1660, col. 1, under "*In vitro* Transduction of *p53*-FLAG Adenovirus"). Viral infection leads to apoptosis mediated cell death. (e.g. p. 1660, col. 2, under "Detection of Apoptosis"; therefore indicating that the transduced cells intrinsically express the *p53* binding receptors (e.g. bp1 or bp2)). In sum, Eicher et al. anticipate the rejected claims.

Conclusion

No claims are allowed. Copies of all newly cited references herein are submitted with this action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ramin (Ray) Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached on Monday- Friday from 8:00-4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

GERRY LEFFERS
PRIMARY EXAMINER

SUGGESTION FOR DEPOSIT OF BIOLOGICAL MATERIAL ATTACHMENT

A declaration by applicant or assignee, or a statement by applicant's agent identifying a deposit of biological material and averring the following may be sufficient to overcome an objection or rejection based on a lack of availability of biological material. Such a declaration:

1. Identifies declarant.

2. States that a deposit of the material has been made in a depository affording permanence of the deposit and ready accessibility thereto by the public if a patent is granted. The depository is to be identified by name and address. (See 37 C.F.R. § 1.803).

3. States that the deposited material has been accorded a specific (recited) accession number.

4. States that all restrictions on the availability to the public of the material so deposited will be irrevocably removed upon the granting of the patent. (See 37 C.F.R. § 1.808(a)(2)).

5. States that the material has been deposited under conditions that assure that access to the material will be available during the pendency of the patent application to one determined by the Commissioner to be entitled thereto under 37 C.F.R. § 1.14 and 35 U.S.C. § 122. (See 37 C.F.R. § 1.808(a)(1)).

6. States that the deposited material will be maintained with all the care necessary to keep it viable and uncontaminated for a period of at least five years after the most recent request for the furnishing of a sample of the deposited microorganism, and in any case, for a period of at least thirty (30) years after the date of deposit or for the enforceable life of the patent, whichever period is longer. See 37 C.F.R. § 1.806).

7. That he/she declares further that all statements made therein of his/her own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the instant patent application or any patent issuing thereon.

Alternatively, it may be averred that deposited material has been accepted for deposit under the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure (e.g., see 961 OG 21, 1977) and that all restrictions on the availability to the public of the material so deposited will be irrevocably removed upon the granting of a patent.

Additionally, the deposit must be referred to in the body of the specification and be identified by deposit (accession) number, date of deposit, name and address of the depository, and the complete taxonomic description.